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LERNER, DAVID, LITTENBERG,
KRUMHOLZ & MENTLIK
600 SOUTH AVENUE WEST
WESTFIELD, NJ 07090

| EXAMINER | |
|---|---|
| SHIAO, REI TSANG | |
| ART UNIT | PAPER NUMBER |
| 1628 | |
| MAIL DATE | DELIVERY MODE |
| 10/29/2010 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/570,849 | TAZI ET AL. | |
| | Examiner | Art Unit | |
| | REI-TSANG SHIAO | 1628 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *15 September 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16 and 27-29* is/are rejected.

7)☒ Claim(s) *17-26* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 March 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/11/08,5/5/08,6/19/08,8/28/08,10/8/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

**1**. This application claims benefit of the foreign applications:

FRANCE 0310460 with a filing date 09/04/2003; and

FRANCE 0400973 with a filing date 02/02/2004.

**2.** Claims 1-29 are pending in the application.

### *Information Disclosure Statement*

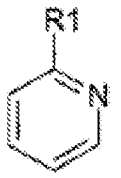
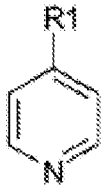
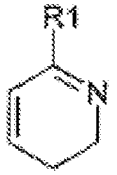
**3**. Applicant's Information Disclosure Statements filed on April 11, 2008, May 05, 2008, June 19, 2008, August 28, 2008 and October 08, 2008 have been considered. Please refer to Applicant's copies of the 1449's submitted herein.

### *Responses to Election/Restriction*

**4.** Applicant's election with traverse of election of Group II claims 1-29, in part, in the reply filed on September 15, 2010 is acknowledged. An election of a compound, i.e., 10-chloro-2,6-dimethyl-2H-pyrido- [3 ' , 4 ' : 4,5] -pyrrolo[2,3-g] -isoquinoline, as a single species is also acknowledged. The traversal is on the ground(s) that applicants submit that it would not be a burden on the Examiner to search for the different aromatic substituents claimed as each have closely related structures. This is found not persuasive, and the reasons are given *infra*.

Claims 1-29 are pending in the application. The scope of the invention of the elected subject matter is as follows.

Claims 1-29, in part, drawn to method of use using compounds of formula (I), wherein the variable X represents N or $N^{+}R4$ thereof, the ring A is in position b

corresponds to  or  or  thereof.

The claims 1-29 herein lack unity of invention under PCT rule 13.1 and 13.2 since the compounds defined in the claims lack a significant structural element qualifying as the special technical feature that defines a contribution over the prior art, see column 1 of Guillonneau et al. US 6,162,811. Accordingly, unity of invention is considered to be lacking and restriction of the invention in accordance with the rules of unity of invention is considered to be proper. Furthermore, even if unity of invention under 37 CFR 1.475(a) is not lacking, which it is lacking, under 37 CFR 1.475(b) a national stage application containing claims to different categories of invention will be considered to have unity of invention if the claims are drawn only to one of the following combinations:

(1) A product and a process specially adapted for the manufacture of said product', or

(2) A product and a process of use of said product; or

(3) A product, a process specially adapted for the manufacture of the said product, and a use of the said product; or

(4) A process and an apparatus or means specifically designed for carrying out the said process; or

(5) A product, a process specially adapted for the manufacture of the said product, and an apparatus or means specifically designed for carrying out the said process.

And, according to 37 CFR 1.475(c)

> if an application contains claims to more or less than one of the combinations of categories of invention set forth in paragraph (b), unity of invention might not be present.

However, it is noted that unity of invention is considered lacking under 37 CFR 1.475(a) and (b). Therefore, since the claims are drawn to more than a product, and according to 37 CFR 1.475 (e)

> the determination whether a group of inventions is so linked as to form a single general inventive concept shall be made without regard to whether the inventions are claimed in separate claims or as alternatives within a single claim.

The claims lack unity of invention and should be limited to only a product, or a process for the preparation, or a use of the said product. In the instant case, Groups I-IV are drawn to various processes of making, and the final products do not contain a common technical feature or structure, and do not define a contribution over the prior art, i.e., similar compound of Guillonneau et al. '811. Moreover, the examiner must perform a commercial database search on the subject matter of each group in addition to a paper search, which is quite burdensome to the examiner.

Claims 1-29, in part, embraced in above elected subject matter, are prosecuted in the case. Claims 1-29, in part, not embraced in above elected subject matter, are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention.

The requirement is still deemed proper and therefore is made FINAL.

***Claim Rejections - 35 USC § 112***

**5**. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-16 and 27-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the instant methods of use using compounds of the formula (I) for treating Frasier syndrome, it does not reasonably provide enablement for the instant methods of use for treating a disease or a certain cancer without limitation (i.e., no named disease), see claims 1, 12-13 or 28. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described. They are:

1. the nature of the invention,

2. the state of the prior art,

3. the predictability or lack thereof in the art,

4. the amount of direction or guidance present,

5. the presence or absence of working examples,

6. the breadth of the claims,

7. the quantity of experimentation needed, and

8. the level of the skill in the art.

In the instant case:

**The nature of the invention**

The nature of the invention is methods of use using compounds formula (I) for treating a disease or a certain cancer without limitation (i.e., no named disease), see claims 1, 12-13 and 28.

**The state of the prior art and the predictability or lack thereof in the art**

The state of the prior art is that the pharmacological art involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific diseases by what mechanism). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic or preventive regimen on its face. Guillonneau et al. US 6,162,811 disclose similar compounds for treating lung carcinoma, see column 20.

The instant claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833,166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

Applicants are claiming intent methods of use using compounds of formula (I) without limitation of a disease or a certain cancer (i.e., no named disease). As such, the specification fails to enable the skilled artisan to use the compounds of claims effective to inhibit or treat various diseases.

In addition, there is no established correlation between *in vitro* or in *vivo* activity and accomplishing treatment of various disease, and those skilled in the art would not accept allegations in the instant specification to be reliable predictors of success, and those skilled in the art would not be able to use compounds of the formula (I) since there is no description of an actual method wherein various disease or a certain cancer related to a pre-messenger RNA splicing process within a cell in a host is inhibited or treated.

Hence, one of skill in the art is unable to fully predict possible results from the administration of the compounds of the formula (I) due to the unpredictability of the various diseases. The "treating a disease or a certain cancer related to a pre-messenger RNA splicing process within a cell" is known to have many obstacles that would prevent one of ordinary skill in the art from accepting treating regimen on its face.

**The amount of direction or guidance present and the presence or absence of working examples**

The only direction or guidance present in the instant specification is the listing of *In vivo* inhibition of the ESE-dependent splicing of GFP (green fluorescent protein) mRNA, see pages 46-58 of the specification. There are no *in vitro* or *in vivo* working

examples present for the treatment of diseases or cancer without limitation by the administration of the instant invention.

**The breadth of the claims**

The breadth of the claims is methods of use of the instant compounds effective to treat a disease or cancer without limitation.

**The quantity of experimentation needed**

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine what diseases or cancer would be benefited (i.e., treated) by the administration of the instant invention and would furthermore then have to determine which of the claimed methods of use would provide treatment of a disease, if any.

**The level of the skill in the art**

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

*in vitro* and *in vivo* screening to determine which methods of use exhibit the desired pharmacological activity and which diseases would benefit from this activity. Thus, the specification fails to provide sufficient support of the broad use of the pharmaceutical compounds of the instant claims for the various diseases.

As a result necessitating one of skill to perform an exhaustive search for which diseases, can be treated by what pharmaceutical compounds of the instant claims in order to practice the claimed invention. Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instantly claimed methods. In view of the breadth of the claim, the chemical nature of the invention, and the lack of working examples regarding the activity of the claimed compounds in regards to the treatment of the many pulmonary disorders, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states that " a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation, with no assurance of success. This rejection can be overcome by incorporation the limitation a disease or cancer supported by the specification into claim 1, 12-13 or 28 would obviate the rejection.

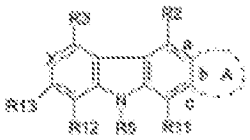
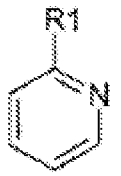
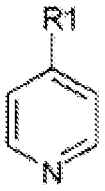
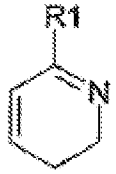
### ***Claim Rejections - 35 USC § 102***

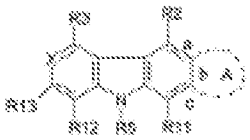
**6**. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-16 and 27-29 are rejected under 35 U.S.C. 102(b) as being anticipated by Chermann et al. CAS: 89:36630.

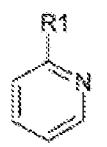
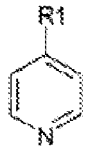
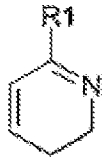
Applicants method of use for treating a disease (e.g., treating cancer) using compounds of formula (I), i.e.,  , wherein the variable X represents N or $N^{+}R4$ thereof, the ring A is in position b corresponds to  or  or  , wherein R1, R4 or R3 is hydrogen or –NH-R8 and R8 is alkyl0N0R9R10 andR9 or R10 is alkyl, see claim 1.

Chermann et al. '630 discloses methods of use (i.e., treating cancer or sarcoma) using two compounds, see RN: 65222-35-7 or 65222-36-8. They clearly anticipate the instant compounds of method of use for treating a disease (e.g., treating cancer) using compounds of formula (I), i.e.,  , wherein the variable X represents N or $N^{+}R4$ thereof, the ring A is in position b corresponds to  , wherein R1,

R4 or R3 is hydrogen or –NH-R8 and R8 is alkyl0N0R9R10 andR9 or R10 is alkyl.

Dependent claims 2-16 and 27-29 are also rejected along with claim 1 under 35 U.S.C. 102(b).

### *Claim Objections*

**7**. Claims 1-29 are objected to as containing non-elected subject matter, i.e., benzo-indole, the ring A is other than  or  ,  , a compound having pyrido[4,3-b] carbazole or benzo[e,f or g] pyrido[4,3-b]indole moiety in claims 5-9, 18-19, and 21-25, etc. It is suggested that applicants amend the claims to the scope of the elected subject matter as defined on the pages 2-3 *supra*.

**8**. Claim 29, line 1, is objected to as containing a typographic error. Replacement of the term "34" with a term "28" would obviate the objection.

### *Conclusion*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rei-tsang Shiao whose telephone number is (571) 272-0707. The examiner can normally be reached on 8:30 AM - 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brandon Fetterolf, can be reached on (571)272-2919. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information

for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/REI-TSANG SHIAO/

Rei-tsang Shiao, Ph.D.
Primary Examiner
Art Unit 1628

October 21, 2010